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A Clinical and Pathologic Study on Para-Aortic Lymph Node Metastasis in Endometrial Carcinoma

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Background: Recent studies have shown that poor survival for patients with early endometrial cancer was related to the extrapelvic spread of the cancer. The purpose of this study was to evaluate the correlation between para-aortic lymph node (PAN) metastasis and histopathologic findings and to assess the clinical utility of identifying PAN metastasis of endometrial carcinoma.

Methods: The correlation of para-aortic lymph node metastasis to the clinical stages of endometrial carcinoma (FIGO, 1982), histopathologic findings, and prognosis were investigated in 200 patients with endometrial carcinoma, who were treated by radical operations, including systematic retroperitoneal lymphadenectomies, between July 1982 and February 1996.

Results: Of these, para-aortic lymph node (PAN) metastasis was seen in 18 (9.0%) and pelvic lymph node (PLN) metastasis in 40 (20.0%). The incidence of PAN metastasis according to clinical stages Ia, Ib, II, and III were 2.5%, 8.5%, 15.7%, and 33.3%, respectively. The incidence of metastasis was significantly higher in stage II than in stage Ia ($P < 0.05$), and in stage III than in stage Ia ($P < 0.01$). PAN metastasis occurred significantly more frequently in the first of each of the following groups: invasion of >½ of the myometrium (15.7%) vs. invasion of <½ of the myometrium (3.6%) ($P < 0.01$), the group with cervical invasion (23.5%) vs. the group without (4.0%) ($P < 0.0001$), the group with lymph-vascular space involvement (17.2%) vs. the group without (1.0%) ($P < 0.0005$), and PLN-metastasis-positive group (40.0%) vs. the negative group (1.3%) ($P < 0.0001$). Multivariate analysis showed a significant correlation between PAN and PLN metastases ($P < 0.0005$). Positive PAN metastasis is not related to multiple PLN metastasis (bilateral PLN metastasis and the number of PLN metastatic groups). However, a correlation was seen between PAN metastasis and common iliac node metastasis. The prognosis was significantly poorer ($P < 0.05$) for patients with both PLN and PAN metastases than for those with PLN metastasis alone.

Conclusions: The results of the present study suggest that PAN metastasis may occur as a consequence of PLN metastasis or the two may occur

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simultaneously as PLN metastasis and also that careful examination of PAN metastasis is necessary to determine the prognosis.

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KEY WORDS: endometrial carcinoma; para-aortic lymph node; lymph node metastasis; pelvic lymph node

INTRODUCTION

Endometrial carcinoma is the third most common gynecologic cancer in Japan. Compared to cervical carcinoma, the incidence of endometrial carcinoma has been increasing in recent years. In three of every four patients, the tumor is clinically confined to the uterus at the time of diagnosis. Although the survival rate is generally high for stage I endometrial carcinoma, recent studies have shown that poor survival for patients with early endometrial carcinoma is related to the extrapelvic spread of the cancer. In 1988, the International Federation of Gynecology and Obstetrics (FIGO) adopted a surgical staging system, which includes assessment for PLN and PAN metastases. Lymph nodes may be ignored, palpated, biopsied, or completely dissected when dealing with endometrial carcinoma. We have systematically performed pelvic lymph node (PLN) and para-aortic lymph node (PAN) dissections. The purpose of this study was to evaluate the correlation between PAN metastasis and histopathologic findings and to assess the clinical utility of identifying PAN metastasis of endometrial carcinoma.

MATERIALS AND METHODS

Between July 1982 and February 1996 (Table I), 200 patients with endometrial carcinoma underwent radical surgical treatment, including systematic pelvic and para-aortic lymphadenectomies, at the Department of Obstetrics and Gynecology of Hokkaido University. Their ages ranged from 23 to 75 years, with a mean of 55.5 years. Treatment was based on the clinical stage (FIGO, 1982). For stage I, a total abdominal hysterectomy was performed from July 1982 to July 1987, which was replaced by modified radical hysterectomy after August 1987. For stage II, a radical hysterectomy was the surgical procedure of choice. In addition, bilateral salpingo-oophorectomy and systematic pelvic and para-aortic lymphadenectomy were performed on all patients. The PAN dissection extended to the inferior mesenteric artery (IMA) in operations performed until March 1988, but after April 1988, it was extended further from the IMA below the renal vein. Chemotherapy (cisplatin 50 mg/m^2, Adriamycin 30 mg/m^2, cyclophosphamide 500 mg/body) was combined with surgery when postoperative histologic examinations revealed deep myometrial invasion or lymph node or adnexal metastasis.

At least two samples were prepared from each dissected lymph node for histologic examination by making an incision on the node along its long axis. The postoperative stages were determined in compliance with the 1988 system proposed by FIGO. Peritoneal cells were collected from 118 patients for cytological examination. Histological differentiation was determined also according to the 1988 FIGO criteria. Statistical significance was determined by employing the Chi-square test. The Kaplan-Meier method was employed to compute the cumulative survival rate, and significant differences in the data were determined by the generalized Wilcoxon test. For multivariate analysis, multiple logistic regression analysis was used.

RESULTS

PLN metastasis was observed in 40 (20.0%) of the 200 patients. The incidence of PLN metastasis increased with the progression of the clinical stage: 8.6% in stage Ia, 18.7% in Ib, 31.4% in II, and 66.7% in III. Significant differences were seen between stages Ia and II ($P < 0.005$) and Ia and III ($P < 0.005$) (Table II). PAN metastasis was observed in 18 of the 200 patients (9.0%). The incidence of PAN metastasis also increased with the progression of the clinical stage: 2.5% in stage Ia, 8.5% in Ib, 15.7% in II, and 33.3% in III. Significant differences were seen between stages Ia and II ($P < 0.05$) and Ia and III ($P < 0.01$) (Table III).

The samples were divided into two groups: A, consisting of adenocarcinoma and adenoacanthoma, and B, consisting of other histological types. Fourteen patients (7.7%) from A and 4 (23.5%) from B exhibited PAN metastases. However, no significant difference was seen between these two groups (Table III).

The incidence of PAN metastasis was inversely related to the degree of histologic differentiation (5.6% for G1, 10.3% for G2, 15.2% for G3), but without statistical significance. Neither was there a significant difference between the incidence of PAN metastasis in patients with or without adnexal metastasis (21.4% and 7.0%, respectively). However, a significant difference in the incidence of PAN metastasis was found in the following groups: involvement of more than half (15.7%) vs. less than half of the myometrium (3.6%) ($P < 0.01$), cervical invasion (23.5%) vs. no invasion (4.0%) ($P < 0.0001$), tumor invasion (17.2%) vs. tumor-free state (1.0%) of the

TABLE I. Patients With Endometrial Carcinoma by Clinical and Surgical Stages, and Histology (n = 200)

	Patients(%)
Clinical stage (FIGO,[a] 1982)	
Ia	81 (40.5)
Ib	59 (29.5)
II	51 (25.5)
III	9 (4.5)
Surgical stage (FIGO,[a] 1988)	
IA	15 (7.5)
B	58 (29.0)
C	30 (15.0)
IIA	3 (1.5)
IIB	10 (5.0)
IIIA	41 (20.5)
C	36 (18.0)
IVA	1 (0.5)
IVB	6 (3.0)
Histology	
Adenocarcinoma	168 (84.0)
Adenoacanthoma	15 (7.5)
Adenosquamous cell carcinoma	9 (4.5)
Clear cell adenocarcinoma	7 (3.5)
Undifferentiated	1 (0.5)

[a]International Federation of Gynecology and Obstetrics.

TABLE II. Clinical Staging and Pelvic Lymph Node Metastasis in Patients With Endometrial Carcinoma

Clinical stage	Metastasis (%)
Ia (N = 81)	7 (8.6)[a]
Ib (N = 59)	11 (18.7)
II (N = 51)	16 (31.4)[b]
III (N = 9)	6 (66.7)[c]
Total (N = 200)	40 (20.0)

a vs. b: $P < 0.005$
a vs. c: $P < 0.005$.

lymph-vascular space ($P < 0.0005$), and positive PLN metastasis (40.0%) vs. metastasis-free PLN (1.3%) ($P < 0.0001$) (Table IV). Multiple logistic regression analysis proved that there was a significant correlation between PAN and PLN metastasis (Table V).

The site most frequently affected was the obturator node, followed by the PAN, internal iliac node, and common iliac node. Only a single lymphatic metastatic site was found in 17 patients, among whom the obturator node was the site of involvement in eight cases (47.1%, Table VI).

PLN metastasis was found in 16 of 18 patients (88.9%) with positive PAN metastasis, whereas in two cases, the metastasis was limited to the PAN (Table VII). The correlation between the number of PAN and PLN metastatic sites was investigated in 40 patients with PLN metastasis. The number of PLN group metastasized was 3.0 ± 2.6 (mean ± SD) in patients with positive PAN metastasis and 1.9 ± 1.0 in those with no metastasis to the PAN. No significant difference was noted between these two groups or among the numbers of metastatic PLN group (Table VIII).

In patients with positive PLN metastasis, PAN metastasis was seen in 57.9% of the cases with bilateral PLN metastasis and in 23.8% of those with unilateral PLN metastasis (Table IX). Positive PAN was found in 66.7% of the patients with positive common iliac nodes. In those with negative common iliac node metastasis, PAN metastasis was found in 24%. There was a significant difference between the two groups (Table IX). PAN metastasis was investigated by dividing the metastatic group according to the sites above and below the inferior mesenteric artery and left and right sections bordering on the right margin of the aorta. The PAN was dissected below the renal vein. Out of 11 patients, the PAN metastasis occurred in the region above the IMA in 7 and only on one side in 8 (72.8%) (Table X).

The cumulative survival rate was compared between those patients with and without positive lymph node metastasis. Eight patients who died of causes other than endometrial cancer were excluded from the accumulation of the survival statistics. The results showed that the prognosis was significantly poorer ($P < 0.01$) for patients with positive PLN and negative PAN metastases when compared to those with negative retroperitoneal lymph node metastasis. The prognosis was also significantly poorer ($P < 0.05$) for those with PLN and PAN metastases than for those with PLN but without PAN metastasis (Fig. 1).

DISCUSSION

Retroperitoneal lymph node metastasis is considered to be one of the major prognostic factors in endometrial carcinoma. Based on the surgical stages determined by FIGO in 1988, endometrial carcinoma has been classified as stage IIIC, not only for PLN but also for PAN metastasis. Recently, much interest has been shown in PAN metastasis in endometrial carcinoma.

Morrow et al. [1] reported that in the Gynecologic Oncology Group study, PAN metastasis was found in 48 (5.4%) of 895 patients with endometrial carcinoma. Other reports have shown positive PAN metastasis in 5.5 to 14.6% of patients with stage I endometrial carcinoma [2–4]. Feuer and Calanog [5] reported that the incidence of PAN metastasis in endometrial carcinoma increased as the disease progressed: 12.7% in stage I, 33.3% in II, and 45.4% in III. The incidence of PAN metastasis was rare in the present study: the results showed it to be 2.5%, 8.5%, 15.7%, and 33.3% in stages Ia, Ib, II, and III, respectively. We examined 200 patients who were treated by systematic lymphadenectomy. Those who underwent incomplete lymphadenectomies were excluded from the study. Creaseman et al. [4] conducted a histopathologic investigation on the disseminating patterns of

TABLE III. Clinical Staging, Histology, and Para-Aortic Lymph Node Metastasis in 200 Patients With Endometrial Carcinoma

	Clinical stage				
Histology	Ia	Ib	II	III	Total
A	1/75 (1.3)	4/53 (7.6)	6/46 (13.1)	3/9 (33.3)	14/183 (7.7)[a]
B	1/6 (16.7)	1/6 (16.7)	2/5 (40.0)		4/17 (23.5)[b]
Total	2/81 (2.5)[c]	5/59 (8.5)	8/51 (15.7)[d]	3/9 (33.3)[e]	18/200 (9.0)

A = adenocarcinoma, adenoacanthoma.
B = adenosquamous cell carcinoma, clear cell adenocarcinoma, undifferentiated carcinoma.
a vs. b: ns, c vs. d: $P < 0.05$, c vs. e: $P < 0.01$.

endometrial carcinoma and reported a significant correlation between PAN metastasis and each of the following risk factors: cancer stage, histology, histologic grade, myometrial invasion, peritoneal cytology, tumor site, adnexal involvement, lymph-vascular space involvement, and other extrauterine metastases.

The results of our study showed a significant correlation with myometrial invasion, cervical invasion, lymph-vascular space involvement, and PLN and PAN metastases, which suggests that endometrial carcinoma with deeper myometrial and cervical invasion is accompanied by increased lymph-vascular space involvement and an increased risk of PAN metastasis.

Autopsy examinations of endometrial carcinoma show a high incidence of positive PAN metastasis. Beck and Latour [6] reported positive node metastasis in 61.1% of patients with endometrial carcinoma. Henriksen [7] reported a 57% incidence of PAN metastasis and that internal iliac nodes and PANs were the most commonly involved lymph nodes in autopsy examinations. Chuang et al. [8] investigated the locations and number of positive lymph nodes in endometrial carcinoma and reported that PANs accounted for the largest percentage (42.8%, 12/28). The results of systematic lymphadenectomy in the present study showed that the obturator nodes were the most common site of involvement in all patients with lymph node metastasis and in patients with a single node metastasis and that there was a high incidence of PAN and internal iliac node metastases.

PAN metastasis was found in 16 (40.0%) of 40 patients with positive PLN metastasis and 2 (1.3%) of 160 patients with negatie PLN metastasis (Table VII). This shows that lymphatic spread to both the PAN and PLN is a frequent occurrence and usually concomitant. Multivariate analysis showed a significant correlation between PAN and PLN metastases. The results of the present study indicate that in endometrial carcinoma, the lymphatic spread of the tumor via the obturator or internal iliac nodes is common and the PAN is a lymph node that is highly vulnerable to tumor metastasis.

As is the case in uterine cervical carcinoma, more than four PLN metastatic sites, bilateral PLN metastasis, and positive common iliac node metastases are proven to be risk factors for PAN metastasis [9]. In the present study,

TABLE IV. Endometrial Carcinoma: Frequency of Para-Aortic Lymph Node Metastasis Among Histologic Factors

Histologic factor	No. of cases with positive lymph node	(%)	*P* value
Grade			
G1	5/89	(5.6)	
G2	8/78	(10.3)	ns
G3	5/33	(15.2)	
Myometrial invasion			
⩽1/2	4/111	(3.6)	<0.01
>1/2	14/89	(15.7)	
Cervical involvement			
Negative	6/149	(4.0)	<0.0001
Positive	12/51	(23.5)	
Adnexal involvement			
Negative	12/172	(7.0)	ns
Positive	6/28	(21.4)	
Lymph-vascular space involvement			
Negative	1/101	(1.0)	<0.0005
Positive	17/99	(17.2)	
Pelvic lymph node metastasis			
Negative	2/160	(1.3)	<0.0001
Positive	16/40	(40.0)	

ns = not significant.

no significant correlation was seen between the incidence of PAN metastasis and the PLN metastatic sites, which were bilateral or multiple. However, metastasis to the common iliac node was found to be associated with ready involvement of the PAN in the metastatic process. Our results suggest that PAN metastasis in endometrial carcinoma may occur as a consequence of or simultaneously with PLN metastasis.

When facing malignant tumors, the examination of patients for lymph node metastasis is considered to be a very important procedure. Lymph node metastasis can be macroscopically verified in only 10–31% of cases with endometrial carcinoma [4,5]. Of metastatic lymph nodes, 39% are <2 mm in diameter [10]. Chuang et al. [8] reported that 39% of nodal metastasis can be verified by microscopic examination. The results of the present study showed that unilateral PAN metastasis occurs frequently at the upper region of the IMA, which indicates the necessity for extensive PAN dissection extending below the renal vein. Thus for pathological confirmation of

TABLE V. Endometrial Carcinoma: Multiple Logistic Regression Analysis of Para-Aortic Node Metastasis

Histologic factors	Parameter estimate	Standard error	Standardized estimate	Odds ratio	*P* value
Myometrial invasion	0.3846	0.3463	0.312749	1.469	0.2667
Cervical invasion	0.0300	0.3820	0.013157	1.030	0.9374
Lymph-vascular space involvement	0.7311	0.4499	0.418895	0.481	0.1042
Pelvic lymph node metastasis	3.8693	0.9628	0.848928	0.021	0.0001

TABLE VI. Sites of Retroperitoneal Lymph Node Metastasis in 200 Patients With Endometrial Carcinoma

	No. of metastasis			
Lymph node	Total(%)	Unilateral	Bilateral	Single
Para-aortic	18 (9.0)	13	5	2
Common iliac	16 (8.0)	11	5	1
External iliac	10 (5.0)	10	0	2
Deep inguinal	5 (2.5)	5	0	1
Internal iliac	18 (9.0)	15	3	3
Obturator	25 (12.5)	18	7	8
Sacral	6 (3.0)	6	0	0
Cardinal	4 (2.0)	3	1	0

TABLE VII. Endometrial Carcinoma: Relationship of Positive Pelvic Nodes to Para-Aortic Nodes

	Pelvic		
Para-aortic	Positive (%)	Negative (%)	Total (%)
Positive	16 (8.0)	2 (1.0)	18 (9.0)
Negative	24 (12.0)	158 (79.0)	182 (91.0)
Total	40 (20.0)	160 (80.0)	200 (100)

TABLE VIII. Endometrial Carcinoma: Para-Aortic Node Metastasis and Number of Pelvic Node Metastatic Groups

Para-aortic node metastasis	Number of metastatic pelvic node groups	Significance
Positive (N = 16)	3.0 ± 2.6	ns
Negative (N = 24)	1.9 ± 1.0	
	(mean ± SD)	

No. of metastatic pelvic node groups	Para-aortic node metastasis	(%)	Significance
1 (N = 15)	4	(26.7)	
2 (N = 11)	4	(36.4)	ns
3≤ (N = 14)	8	(57.1)	

ns = not significant

TABLE IX. Endometrial Carcinoma: Para-Aortic Node Metastasis and Pelvic Node Metastasis

	Para-aortic node metastasis	(%)	Significance
Pelvic node metastasis			
Bilateral (N = 19)	11	(57.9)	ns
Unilateral (N = 21)	5	(23.8)	
Common iliac node metastasis			
Positive (N = 15)	10	(66.7)	<0.05
Negative (N = 25)	6	(24.0)	

ns = not significant

TABLE X. Sites of Para-Aortic Node Metastasis in Endometrial Carcinoma

	Para-aortic node metastasis		
	Unilateral	Bilateral	Total
Lower site of IMA[a]	3 (27.3)	1 (9.0)	4 (36.3)
Upper site of IMA[a]	2 (18.2)	0 (0.0)	2 (18.2)
Both sites	3 (27.3)	2 (18.2)	5 (45.5)
Total	8 (72.8)	3 (27.2)	11 (100.0)

[a]Inferior mesenteric artery.

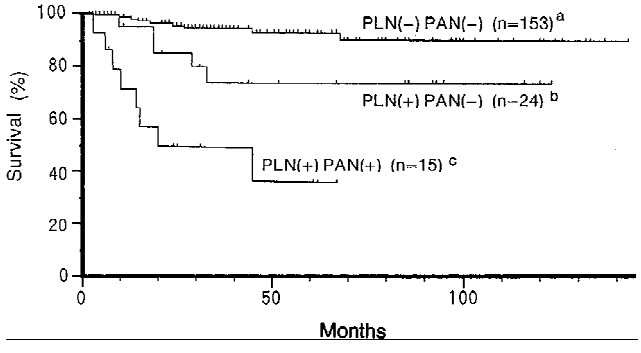

Fig. 1. Survival of 192 patients with endometrial carcinoma (Kaplan-Meier method, generalized Wilcoxon test). Eight patients who died from causes other than endometrial cancer were deleted from the calculation of the survival statistics. PLN: pelvic lymph node metastases; PAN: para-aortic lymph node metastases. a vs. b: $P < 0.01$; a vs. c: $P < 0.0001$; b vs. c: $P < 0.05$.

lymph node metastasis, it is believed that a systematic lymphadenectomy that includes the PAN is necessary.

The therapeutic efficacy of PAN dissection is reported to be very low [11,12]. Others have reported that the survival rate was higher for the group in which lymph node dissection was performed in contrast to the group in which no dissection was performed [13,14]. Rose et al. [15] reported that 9 of 17 patients (53%) with PAN metastasis survived following radiation therapy. Potish et al. [16] investigated the 5-year survival rate of 48 patients following radiation therapy and reported metastasis to the PLN in only 67%, only to the PAN in 47%, and 43% to both the PLN and PAN. Although the operating time for a PAN dissection is generally longer than that required for the standard procedure, lymph node dissection

(including PAN dissection) produces no notable differences in the need for blood transfusion, the development of fever, postoperative complications, or mortality [17,18].

The results of the present study showed a cumulative 5-year survival rate of 93.7% in patients with PLN and PAN negative metastasis, 74.5% in those with positive metastasis only to the PLN, and 37.9% with positive PLN and PAN metastases. The prognosis is evidently poorer for patients with PLN metastasis associated with PAN involvement, in contrast to those with PLN metastasis but without PAN metastasis. Therefore we believe that it is very important to examine patients for PLN and PAN metastases for a more reliable prognosis.

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